IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ashley J. Birkett	) PATENT
Serial No.:	09/930,915	) Attorney Docket
		) ICC-102.2
Filed:	August 15, 2001	) (4564/81175)
		)
For:	IMMUNOGENIC HBc CHIMER PARTICLES HAVING ENHANCED STABILITY	)
		) Group Art No. 1648
Examiner:	Donna C. Wortman	)

REPLY AND AMENDMENT

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Action mailed on January 9, 2004, please amend the application as follows.

1. (currently amended) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that

(a) contains an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop~~, or a sequence of at least about 135 residues of the N terminal 150 HBc amino acid residues~~,

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contains a sequence of at least 5 amino acid residues from HBc position 135 to the HBc C-terminus,

said chimer molecules (i) containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles being more stable than are particles formed from an otherwise identical HBc chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue.

2. (original) The recombinant HBc chimer protein molecule according to claim 1 wherein said peptide-bonded

heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

3. (original) The recombinant HBc chimer protein molecule according to claim 2 wherein said heterologous epitope is a B cell epitope.

4. (original) The recombinant HBc chimer protein molecule according to claim 3 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

5. (original) The recombinant HBc chimer protein molecule according to claim 3 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

6. (original) The recombinant HBc chimer protein molecule according to claim 5 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

7. (original) The recombinant HBc chimer protein molecule according to claim 2 further including a peptide-bonded heterologous T cell epitope.

8. (original) The recombinant HBc chimer protein molecule according to claim 7 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

9. (original) The recombinant HBc chimer protein molecule according to claim 8 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

10-11. (cancelled)

12. (original) The recombinant HBc chimer protein molecule according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope.

13. (original) The recombinant HBc chimer protein molecule according to claim 12 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present.

14. (original) The recombinant HBc chimer protein molecule according to claim 13 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope.

15. (original) The recombinant HBc chimer protein molecule according to claim 14 that contains the HBc amino acid residue sequence of position 1 through at least position 140, plus a single cysteine residue at the C-terminus.

16. (original) The recombinant HBc chimer protein molecule according to claim 15 wherein said chimer contains the HBc amino acid residue sequence of position 1 through position 149.

17. (original) The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

18. (currently amended) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 135 to about 515 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) ~~the sequence of HBc at positions 76 to 85 is present~~

~~free from heterologous residues, or (iii)~~ one or more of residues 76 to 85 is absent;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) zero through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii),

said chimer self-assembling into particles on ~~expression in a host cell, said particles being~~ substantially free of binding to nucleic acids and more stable than are particles formed from an otherwise identical HBc chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer.

19. (original) The recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes.

20. (original) The recombinant HBc chimer protein molecule according to claim 19 wherein said two

heterologous epitopes are present in Domains I and II, II and IV or I and IV.

21. (original) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope.

22. (original) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a T cell epitope.

23. (original) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope and the other is a T cell epitope.

24. (original) The recombinant HBc chimer protein molecule according to claim 18 wherein said Domain I includes a heterologous epitope peptide-bonded to one of HBc residues 1-4.

25. (original) The recombinant HBc chimer protein molecule according to claim 24 wherein said heterologous epitope of Domain II is a B cell epitope.

26. (original) The recombinant HBc chimer protein molecule according to claim 25 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

27. (original) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope.

28. (original) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope comprises up to about 245 amino acid residues.

29. (original) The recombinant HBc chimer protein molecule according to claim 28 wherein said heterologous epitope is a B cell epitope.

30. (original) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 6 to about 50 amino acid residues.

31. (original) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

32. (original) The recombinant HBc chimer protein molecule according to claim 27 wherein said Domain IV comprises 1 to about 5 cysteine residues within about 30 residues from the C-terminus of the chimer molecule.

33. (original) The recombinant HBc chimer protein molecule according to claim 27 wherein the HBc

sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

34. (cancelled)

35. (original) The recombinant HBc chimer protein molecule according to claim 18 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

36. (original) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous linker residue for a conjugated epitope.

37. (original) The recombinant HBc chimer protein molecule according to claim 36 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

38. (original) The recombinant HBc chimer protein molecule according to claim 37 that contains a single cysteine residue at the C-terminus of the HBc chimer protein molecule.

39-41. (cancelled)

42. (original) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about

175 to about 240 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) a cysteine residue [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said chimer self-assembling into particles on expression in a host cell that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.2 to about 1.6 and are more stable than are particles formed from an otherwise identical HBc chimer molecule that lacks said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 5 percent of the amino

acid residues are substituted in the HBc sequence of the chimer.

43. (original) The recombinant HBc chimer protein molecule according to claim 42 wherein said heterologous epitope of Domain II is a B cell epitope.

44. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 15 to about 50 amino acid residues.

45. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

46. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

47. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein said B cell epitope is an amino acid sequence present in a pathogen selected from the group consisting of *Streptococcus pneumonia, Cryptosporidium parvum,* HIV, foot-and-mouth disease virus, influenza virus, *Yersinia pestis, Haemophilus influenzae, Moraxella catarrhalis, Porphyromonas gingivalis, Trypanosoma cruzi, Plasmodium falciparum, Plasmodium vivax, Plasmodium berghi, Plasmodium yoelli, Streptococcus sobrinus, Shigella flexneri,* RSV,

Plasmodium Entamoeba histolytica, Schistosoma japonicum, Schistosoma mansoni, bovine inhibin and ebola virus.

48. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

49. (original) The recombinant HBc chimer protein molecule according to claim 48 wherein said T cell epitope is from the organism against which a contemplated chimer is to be used as an immunogen.

50. (original) The recombinant HBc chimer protein molecule according to claim 43 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule.

51. (original) An immunogenic particle comprising ~~comprised of~~ recombinant hepatitis B core (HBc) chimeric protein molecules, said chimeric protein (i) displaying one or more immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or (ii) having a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop, and containing a cysteine residue at or near the C-terminus, said particle being substantially free of nucleic acid binding and exhibiting enhanced stability relative to particles comprised of otherwise identical proteins that are free of said cysteine residue.

52. (original) The immunogenic particle according to claim 51 that exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7.

53. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the N-terminus.

54. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the C-terminus.

55. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope in the immunogenic loop.

56. (currently amended) The immunogenic particle according to claim ~~1~~ 51 whose recombinant HBc chimeric protein displays a B cell immunogenic epitope.

57. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays a T cell immunogenic epitope.

58. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays separate B cell and T cell immunogenic epitopes.

59. (original) The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop.

60. (original) The immunogenic particle according to claim 59 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

61. (original) The immunogenic particle according to claim 60 wherein said heterologous linker residue for a conjugated epitope is conjugated to a hapten.

62. (original) The immunogenic particle according to claim 61 wherein said hapten is an oligosaccharide.

63. (original) An immunogenic particle comprising ~~comprised of~~ a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules;

said recombinant chimeric HBc protein molecules having a length of up to about 515 amino acid residues that

(a) contain a HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues,

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contain a sequence of at least 6 amino acid residues from HBc position 135 to the HBc C-terminus,

said chimer molecules containing no more than 10 percent conservatively substituted amino acid residues in the HBc sequence, and

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from an otherwise identical HBc chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 20 percent of the amino acid residues are substituted in the HBc sequence of the chimer.

64. (original) The immunogenic particle according to claim 63 that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6.

65. (original) The immunogenic particle according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is about 175 to about 240 amino acid residues.

66. (original) The immunogenic particle according to claim 63 wherein said peptide-bonded

heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

67. (original) The immunogenic particle according to claim 66 wherein said heterologous epitope is a B cell epitope.

68. (original) The immunogenic particle according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is up to about 435 amino acid residues.

69. (original) The immunogenic particle according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

70. (original) The immunogenic particle according to claim 68 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

71. (original) The immunogenic particle according to claim 70 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

72. (original) The immunogenic particle according to claim 68 further including a peptide-bonded heterologous T cell epitope.

73. (original) The immunogenic particle according to claim 72 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

74. (original) The immunogenic particle according to claim 73 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

75. (original) The immunogenic particle according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 135 to about 515 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all of the residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBc at positions 76 to 85 is present free from heterologous residues;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) zero through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten ceyteine residues of (ii), said chimeric HBc protein having an amino acid residue sequence in which no more than about 10 percent of the amino acid residues are substituted in the HBc sequence.

76. (original) The immunogenic particle according to claim 75 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.

77. (original) The immunogenic particle according to claim 76 wherein said hapten is a B cell immunogen.

78. (original) The immunogenic particle according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino

acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to about five cysteine residues [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6, and said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence.

79-115. (cancelled)

RESPONSE UNDER 37 C.F.R. §1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1648

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ashley J. Birkett	Attorney Docket: ICC-103.1 US 83502
Serial No.:	09/931,325	
Filed:	August 15, 2001	
For:	Malaria Immunogen and Vaccine	Group Art Unit 1648
Examiner:	Zachariah Lucas	

SECOND REPLY AND AMENDMENT AFTER FINAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Advisory Action mailed January 28, 2004 and in further reply to the Official Action mailed October 20, 2003, please amend the above-identified application as follows.

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 140 to about 310 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of~~ the parasite *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79, said B cell epitope being comprised of two to about five repeats of the amino acid residue sequence Asn-Ala-Asn-Pro;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, (iii) fewer than

three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that at least five amino acid residues are present of the amino acid residue sequence from position 136 through 149, when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present, and wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

2. (Original) The recombinant HBc chimer protein molecule according to claim 1 present as self-assembled particles.

3, 4, 5. (Cancelled).

6. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein Domain I consists essentially of the HBc sequence from position 1 through position 75.

7. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein Domain II independently includes zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

8. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein said sequence heterologous to HBc at position 150 to the C-terminus of

Domain IV comprises an amino acid residue sequence that constitutes a T cell epitope of the same species of *Plasmodium* as said B cell epitope.

9. (Currently Amended) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a sequence of about 155 to about 235 amino acid residues that contains four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through 75 of HBc;

(b) Domain II is about 18 to about 46 residues in length of which (i) 10 residues are present in a sequence of HBc at positions 76 to 85 and (ii) a sequence of 8 to about 36 residues that constitute a repeated B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ of the sequence Asn-Ala-Asn-Pro that is peptide-bonded between the residues of positions 78 and 79, said B cell epitope being comprised of two to about five repeats of an amino acid residue sequence, said Domain independently including zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of~~ comprises the HBc sequence from position 86 through position 135; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) ~~zero~~ one to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof

adjacent to each other, and (iv) up to 50 amino acid residues in a sequence that constitutes a T cell epitope of *Plasmodium falciparum* ~~the same species of *Plasmodium* as said B cell epitope~~ peptide-bonded to the final HBc amino acid residue present in the chimer, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

10. (Original) The recombinant HBc chimer protein molecule according to claim 9 wherein Domain IV comprises one amino acid residue to a sequence of about nine amino acid residues of the HBc sequence from residue position 141 through about position 149 peptide-bonded to residue 140.

11. (Original) The recombinant HBc chimer protein molecule according to claim 10 wherein Domain IV consists essentially of a sequence of nine amino acid residues of the HBc sequence from residue position 141 through position 149 peptide-bonded to residue 140.

12, 13. (Cancelled).

14. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 9 ~~13~~ wherein the repeated sequence of said B cell epitope of Domain II is repeated three or four times.

15. (Original) The recombinant HBc chimer protein molecule according to claim 14 wherein the repeated

sequences are peptide-bonded to each other without interruption.

16. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 15 wherein said B cell epitope includes a second CS protein sequence from ~~the same~~ *Plasmodium falciparum* ~~species~~ that is peptide-bonded to said repeated sequence.

17. (Original) The recombinant HBc chimer protein molecule according to claim 16 wherein said second CS protein sequence is Asn-Val-Asp-Pro.

18. (Cancelled).

19. (Original) The recombinant HBc chimer protein molecule according to claim 17 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

20. (Original) The recombinant HBc chimer protein molecule according to claim 16 wherein said second CS protein sequence is SEQ ID NO:126 (Asn-Ala-Asn-Pro-Asn-Val-Asp-Pro).

21. (Cancelled).

22. (Original) The recombinant HBc chimer protein molecule according to claim 20 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

23. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 10 wherein said one to three cysteine residues are present in Domain IV within about 30 residues of the carboxy-terminus of the chimeric molecule.

24. (Original) The recombinant HBc chimer protein molecule according to claim 23 wherein said one to three cysteine residues are present in said T cell epitope.

25. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 24 wherein said T cell epitope is present and has the sequence of SEQ ID NO: 148 or 24 ~~25~~ (EYLNKIQNSLSTEWSPCSVT OR GIEYLNKIQNSLSTEWSPCSVT~~-YLDKVRATVGTEWTPCSVT~~).

26. (Original) The recombinant HBc chimer protein molecule according to claim 9 present as self-assembled particles.

27. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 155 to about 235 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the

sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of~~ the parasite *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79, said B cell epitope being comprised of two to about five repeats of an amino acid residue sequence Asn-Ala-Asn-Pro;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III, and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, ~~(ii) zero to three cysteine residues,~~ (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus ~~with the proviso that at least five amino acid residues are present of the HBc amino acid residue sequence from position 136 through 149 when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present~~, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

28. (Original) The particles according to claim 27 whose HBc chimer protein molecules have a sequence length of about 165 to about 210 amino acid residues.

29, 30, 31. (Cancelled).

32. (Original) The particles according to claim 27 wherein Domain I consists essentially of the HBc sequence from position 1 through position 75.

33. (Original) The particles according to claim 27 wherein Domain II independently includes zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

34. (Currently Amended) The particles according to claim 27 wherein said sequence heterologous to HBc at position 150 to the C-terminus of Domain IV comprises an amino acid residue sequence that constitutes a T cell epitope of *Plasmodium falciparum* ~~the same species of *Plasmodium* as said B cell epitope~~.

35. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being comprised of two to about five repeats of the ~~an~~ amino acid residue sequence Asn-Ala-Asn-Pro, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises the HBc sequence of residues 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 140 through 149 peptide-bonded to the residue of position 140, (ii) ~~zero~~ one to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 25 amino acid residues in a sequence that constitutes a T cell epitope of the same species of *Plasmodium* as said B cell epitope, said T cell epitope sequence being peptide-bonded to the final HBc amino acid residue present in a chimer molecule or a cysteine residue, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

36. (Currently Amended) The particles according to claim 35 wherein Domain IV comprises one to a sequence of nine amino acid residues of the HBc sequence from residue position 141 through position 149 linked between residue 140 of said Domain III sequence and a *Plasmodium falciparum* ~~*or Plasmodium vivax*~~ T cell epitope.

37. (Original) The particles according to claim 36 wherein the nine amino acid residues of the HBc sequence from residue position 141 through position 149 are present.

38, 39. (Cancelled).

40. (Original) The particles according to claim 39 wherein the repeated sequence of said B cell epitope of Domain II is repeated three or four times.

41. (Original) The particles according to claim 40 wherein the repeated sequences are peptide-bonded to each other without interruption.

42. (Currently Amended) The particles according to claim 41 wherein said B cell epitope includes a second CS protein sequence from *Plasmodium falciparum* ~~the same *Plasmodium species*~~ that is peptide-bonded to said repeated sequence.

43. (Original) The particles according to claim 42 wherein said second CS protein sequence is Asn-Val-Asp-Pro.

44. (Original) The particles according to claim 43 wherein said second CS protein sequence is peptide-bonded at the carboxy-terminus of said repeated sequence.

45. (Original) The particles according to claim 43 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

46. (Original) The particles according to claim 42 wherein said second CS protein sequence is SEQ ID NO:126 (Asn-Ala-Asn-Pro-Asn-Val-Asp-Pro).

47. (Original) The particles according to claim 46 wherein said second CS protein sequence is peptide-bonded at the carboxy-terminus of said repeated sequence.

48. (Original) The particles according to claim 46 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

49. (Original) The particles according to claim 35 wherein said B cell epitope of *Plasmodium falciparum* has an amino acid residue sequence selected from the group consisting of SEQ ID NOs:1-14.

50. (Cancelled).

51. (Original) The particles according to claim 35 wherein said T cell epitope of *Plasmodium falciparum* is present and has the amino acid residue sequence of SEQ ID NO:24.

52. (Cancelled).

53. (Currently Amended) The particles according to claim 36 ~~further including~~ wherein said one to three cysteine residues in the Domain IV sequence are present within about 30 residues of the carboxy-terminus of the chimeric molecule.

54. (Original) The particles according to claim 53 having one cysteine residue in the Domain IV sequence.

55. (Cancelled).

56. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contain four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence that constitutes a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~*or Plasmodium vivax*~~ is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being selected from the group consisting of SEQ ID NOs: 1-14 ~~1-21~~, said Domain II including two peptide-bonded residues on either side of said B cell

epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide bonded to residue 85; and

(d) Domain IV comprises the sequence of HBc residues 136-140 peptide-bonded to residue 135 plus one to nine residues of a HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 140 and also peptide-bonded to a *Plasmodium falciparum* ~~*or Plasmodium vivax*~~ T cell epitope of a sequence of up to about 25 amino acid residues that includes a cysteine residue, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

57. (Currently Amended) The particles according to claim 56 wherein Domain IV comprises nine amino acid residues of the HBc sequence from residue position 141 through position 149 bonded between said residue 140 and said *Plasmodium falciparum* ~~*or Plasmodium vivax*~~ T cell epitope.

58. (Currently Amended) The particles according to claim 57 wherein ~~said B cell epitope is of the CS protein of *Plasmodium falciparum* that is selected from the group consisting of SEQ ID NOs:1-14 and~~ said *Plasmodium falciparum* T cell epitope has the amino acid sequence of SEQ ID NO:24.

59. Cancelled.

60. (Currently Amended) A vaccine or inoculum comprising an immunogenic effective amount immunogenic particles dissolved or dispersed in a pharmaceutically acceptable diluent, wherein said immunogenic particles are comprised of a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules having a length of about 140 to about 310 amino acid residues that contain four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of~~ the parasite *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79, said B cell epitope being comprised of two to about five repeats of the amino acid residue sequence Asn-Ala-Asn-Pro;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of

position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, ~~(ii) zero to three cysteine residues,~~ (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, ~~with the proviso that at least five amino acid residues are present of the amino acid residue sequence from position 136 through 149, when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present,~~ and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

61. (Currently Amended) The vaccine or inoculum according to claim 60 wherein said immunogenic particles are those having a sequence of about 165 to about 210 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope

being comprised of two to about five repeats of ~~an~~ the amino acid residue sequence Asn-Ala-Asn-Pro, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises the HBc sequence of residues 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) nine residues of a HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 140, (ii) one to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) a *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ T cell epitope, said T cell epitope sequence being peptide-bonded to the final HBc amino acid residue present in a chimer molecule or a cysteine residue, and

wherein no more than 5 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

62. (Previously Presented) The vaccine or inoculum according to claim 60 wherein Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being

comprised of three or four repeats of an amino acid residue sequence Asn-Ala-Asn-Pro, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

63. (Currently Amended) The vaccine or inoculum according to claim 62 wherein the repeated sequences are peptide-bonded to each other without interruption and wherein said B cell epitope includes a second CS protein sequence from *Plasmodium falciparum* ~~the same *Plasmodium* species~~ that is peptide-bonded to said repeated sequence.

64. (Currently Amended) The vaccine or inoculum according to claim 60 wherein said immunogenic particles are those comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contain four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence that constitutes a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being selected from the group consisting of SEQ ID NOs:1-14~~1-21~~, said Domain II including two peptide-

bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide bonded to residue 85; and

(d) Domain IV comprises the sequence of HBc residues 136-140 peptide-bonded to residue 135 plus nine residues of a HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 140 and also peptide-bonded to a *Plasmodium falciparum* T cell epitope of a sequence of up to about 25 amino acid residues that includes a cysteine residue, and

wherein no more than 5 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

65. (Currently Amended) The vaccine or inoculum according to claim 64 wherein said immunogenic particles are those wherein ~~said B cell epitope is of the CS protein of Plasmodium falciparum that is selected from the group consisting of SEQ ID NOs:1-14 and~~ said *Plasmodium falciparum* T cell epitope has the amino acid sequence of SEQ ID NO:24.

66. (Cancelled).

67. (Original) The vaccine or inoculum according to claim 60 that is adapted for parenteral administration.

68-75. (Cancelled).